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US Patent and Trademark Office  
US Department of Commerce  
Appn. Number: 10/007,489  
Appn. Filed: 12/05/2001  
Applicant: Elizabeth Gay Frayne

Title: "Microbial Production of Phosphorothioate Substituted DNA, RNA, and Oligo Mixtures"

Examiner: Devesh Khare, PhD, JD  
Art Unit: 1623

RE: Office Action Summary issued Oct. 18<sup>th</sup> for Application No. 10/007,489

Dear Sir,

In response to your office action I have made the claims 1 and 5 more definite and suited to describe the active steps of the process invention. Please amend as follows:

1. A process for generating phosphorothioate substituted nucleic acids in vivo

comprising:

- 1) preparing microbial culture media depleted of phosphate
- 2) adding thio-phosphate as an alternative source of phosphate to the media
- 3) culturing micro-organisms in the modified media containing thiophosphate  
such that thiophosphate enters into nucleotide precursor pools thereby  
enabling the synthesis of phosphorothioate internucleotide linkages.

5. The method of claim 1 where the alternative source of phosphate is a  
derivative of thiophosphate such as dithiophosphate or methylthiophosphate.